factor, applying an extracelluar matrix component, applying a virus, applying an electroporation, applying an antisense polynucleotide, applying a gene knock-out, applying a gene overexpression, applying a gene mutation, applying a cell fusion, and combinations thereof;

code for determining at least one of a plurality of features of a first component of said at least two of a plurality of components and at least one of a plurality of features of a second component of said at least two of a plurality of components;

code for determining a plurality of descriptors, wherein said descriptors comprise at least one said plurality of features of said first component or at least one of a plurality of features of said second component and wherein at least one of said plurality of descriptors is formed by combining features of said first component and said second component;

code for searching a plurality of descriptors obtained from a database to locate descriptors based upon one of said descriptors of said manipulation, said searching forming a plurality of located descriptors;

code for determining, based upon said located descriptors, properties of said manipulation based upon said located descriptors; and

a computer readable storage medium for holding the codes.

50. (Amended) The computer program product of claim 49 wherein said plurality of components are independently selected from the group consisting of a protein, a protein modification, a nucleic acid, a lipid, a carbohydrate, a sub-cellular structure, and an organelle.

REMARKS

Applicants respectfully request reconsideration of the rejections set forth in the Office Action mailed on February 14, 2001. Claims 1-12, 19-41, 44 and 45 have been rejected. Claims 1-12, 19-41, 44 and 45 have been cancelled herein. Claims 56-65 have been added herein. Accordingly, Claims 49-65 are now pending.

Applicants note with appreciation the withdrawal of the objections to Claims 37, 45 and 48; the rejection of Claims 6, 7 and 40-45 under 35 U.S.C. §112, second paragraph; the rejection of Claims 1-5, 8-12, and 17-48 under 35 U.S.C. §102(b) as being anticipated by Pauwels et al. (1997) J. Pharmacol. and Toxicol. Methods 37:105-115 ("Pauwels"); and the rejection of Claim

31 under 35 U.S.C. §103(a) as being unpatentable over Pauwels in view of Weinstein et al. (197) Science 275:343-349 ("Weinstein").

Applicants also note that the Office Action Summary mailed on February 14, 2001 indicates that Claims 1-12, 19-41, 44 and 45 are pending. However, Applicants added Claims 49-55 in the Amendment filed on December 19, 2000. Although these claims were inadvertently omitted from the Office Action, Applicant will address the Examiner's rejections as applied to them.

This amendment is to expedite prosecution and should not be construed as acquiescence in any ground of rejection. Applicants reserve the right to prosecute the originally filed claims in the future. A clean version of the amended claims with instructions for entry pursuant to 37 C.F.R. §1.121(c)(1)(i) is included above. A marked-up version of the amended claims pursuant to 37 C.F.R. §1.121(c)(1)(ii) is attached as Appendix I. The comments in the Office action are now addressed in turn.

Rejections under 35 U.S.C. § 102

Claims 1-6 and 8-10 have been rejected under 35 U.S.C. § 102(b) as being anticipated by PCT WO 97/45730 ("Biodx"). The rejection is respectfully traversed as applied to the newly added claims.

As repeatedly indicated by the courts, anticipation requires that all of the elements and limitations of the claim be found within a single prior art reference. There must be no difference between the claimed invention and the disclosure provided by the reference, as viewed by a person of ordinary skill in the field of the invention. (*Scripps Clinic & Research Fdtn. v. Genentech, Inc.*, 927 F.2d 1565, 1576 [Fed. Cir. 1991]). Furthermore, "[t]o establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. (*In re Royka*, 490 F.2d 981, 180 USPQ 580 [CCPA 1974]). Applicants submit that Biodx does not teach every element of the claims; therefore, that the invention, as claimed herein, is not anticipated by Biodx.

The present invention, as claimed herein, relates to a computer program product for determining a property of a manipulation on one or more cell lines. More specifically, cell lines are manipulated with one or more factors. The effects of such manipulations on at least two components of the cells are quantified and/or qualified through the use of descriptors which can be combined into "cellular fingerprints". Such fingerprints can be analyzed, classified and/or

compared using a plurality of techniques, such as statistical classification and clustering, heuristic classification techniques, a technique of creating "phylogenetic trees" based on various distance measures between cellular fingerprints.

In a presently preferred embodiment, the descriptors can comprise morphometric, frequency, multi-dimensional parameters and the like, extracted from one or more fluorescence images taken from a number of cellular markers from a population of cells. Such descriptors comprise a unique "fingerprint" that can be incorporated into a database. Such cellular fingerprints will change according to the nature of the manipulation. Such changes are sufficiently unique to permit a correlation to be drawn between similar fingerprints. In a presently preferred embodiment, a database can be built from a plurality of such fingerprints from different cell lines and different manipulations thereof.

Biodx describes a computer-implemented method for analyzing cells wherein cells containing reporter molecules are scanned with a fluorescence microscope. The optical information is converted into digital data which is then used to determine the distribution, environment or activity of the labeled reporter molecules in the cells. A database is provided for storage and retrieval of data from each experiment. See, page 39, lines 6-11. Significantly, Biodx does not teach or suggest any methods for comparing data from one experiment with that from another. Biodx does not teach or suggest the use of image analysis techniques employing techniques such as multidimensional representations, frequency-based representations, multidimensional cluster analysis techniques, and the like. Biodx does not teach or suggest any methods for creating "fingerprints" that quantify and/or qualify the effects of a manipulation on a cell line or methods for comparing one fingerprint to another.

As the elements of Biodx are *not* the same as those presently claimed, Applicants submit that Biodx does not anticipate the pending claims and respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-6 and 8-10 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Biodx in view of Weaver *et al.* U.S. Patent No. 4,959,301 ("Weaver"). In addition, Claims 1-6 and 8-10 been rejected under 35 U.S.C. 103(a) as being unpatentable over Biodx in view of Singhvi *et al.* U.S. Patent No. 5,776,748 ("Singhvi"). Claims 1-6, 8-12, 17-30, 32-41, 44, and 45 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Biodx in view of Weaver or Biodx and Singhvi and further in view of Pauwels. Claims 1-6, 8-12, 17-41, 44 and 45 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Biodx, Weaver and Pauwels or

Biodx, Singhvi and Pauwels and further in view of Weinstein. This rejection is respectfully traversed as applied to the amended claims.

Biodx is cited as above. Weaver is cited as teaching the application of an electromagnetic stimulus which would result in electroporation. Singhvi is said to describe the treatment of cells with radiation. Pauwels is said to teach a method comprising exposing neoplastic cell lines with drugs of various pharmacological classes, monitoring drug-induced modifications by means of a digital cell image analysis of *one cellular component* (i.e., nuclear DNA) to create databases, submitting numerical data quantitative describing chromatin patterns to multivariate analysis with canonical transformation of the data. Weinstein is cited for its teaching of the use of gene expression profiling in screening a panel of cancer cell lines.

As discussed above, the claims have been amended herein to focus on a particularly preferred embodiment of the invention, namely, the creation of cellular fingerprints reflecting the effects of manipulations on two or more components of cells and the analysis of such fingerprints whereby the effects of manipulations can be clustered or otherwise statistically analyzed. None of the cited references teach or suggest this limitation, and so they cannot be combined to render the pending claims obvious. None of the secondary references cure the lack of suggestion of the primary reference to perform multivariate analysis on the effects of cellular manipulations on two or more cellular components.

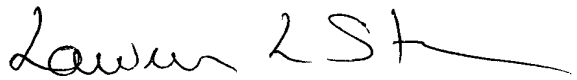
Applicants assert that by suggesting that the cited art may be used to produce the presently claimed invention, the Examiner presents, in essence, an "obvious to experiment" or "obvious to try" standard for obviousness. The "obvious to try" standard has been thoroughly discredited by the courts. Indeed, an obviousness rejection is inappropriate, where the prior art gives no indication of which parameters are critical or no direction as to which of many choices is likely to be successful. *In re O'Farrell*, 7 USPQ2d 1673, 1681 Fed. Cir. 1988. "Both the suggestion and the expectation of success must be founded in the prior art, and not in applicant's disclosure." *In re Dow Chemical*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). There is simply no suggestion in the cited references regarding the advantages in performing multivariate analyses on multiple cellular components (as opposed to the single marker used in Pauwels). Thus, there is nothing in the cited prior art that would provide one of ordinary skill in the art with the knowledge necessary to develop the claimed inventions.

For these reasons, withdrawal of the rejections is respectfully requested.

Conclusion

The Applicant respectfully maintains that all pending claims are in condition for allowance. Therefore, the Applicant respectfully requests a Notice of Allowance for this Application from the Examiner. Should any unresolved issues remain, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,
BEYER WEAVER & THOMAS, LLP



Lauren L. Stevens
Reg. No. 36,691

P.O. Box 778
Berkeley, CA 94704-0778

MARKED UP VERSION OF AMENDED CLAIMS

49. (Amended) A computer program product for determining a property of a manipulation based upon **determination of** effects of said manipulation on at least two of a plurality of components of at least one of a plurality of cells, said computer program product comprising:

code for **[providing] receiving one or more images of [at least one of a plurality of samples of said manipulation to said]** at least **two of a plurality of components of at least** one of a plurality of cells **that have been exposed to the manipulation**, wherein said manipulation is selected from the group consisting of applying a hormone, applying a growth factor, applying an extracelluar matrix component, applying a virus, applying an electroporation, applying an antisense polynucleotide, applying a gene knock-out, applying a gene overexpression, applying a gene mutation, applying a cell fusion, and combinations thereof;

code for determining at least one of a plurality of features of **a first component of** said at least two of a plurality of components **and at least one of a plurality of features of a second component of said at least two of a plurality of components [of at least one of a plurality of cells in the presence of said manipulation]** ;

code for determining **[at least one of]** a plurality of descriptors**, wherein said descriptors comprise at least one said plurality of features of said first component or at least one of a plurality of features of said second component and wherein at least one of said plurality of descriptors is formed by combining features of said first component and said second component [, said descriptors comprising at least one of said plurality of features]** ;

code for searching a plurality of descriptors obtained from a database to locate descriptors based upon one of said descriptors of said manipulation, said searching forming a plurality of located descriptors;

code for determining, based upon said located descriptors, properties of said manipulation based upon said located descriptors**[;**

wherein said two of a plurality of components includes a first component and a second component of a cell, said code for determining at least one of a plurality of descriptors of a state comprises code for combining information about said first component and said second component]; and

a computer readable storage medium for holding the codes.

50. (Amended) The computer program product of claim 49 wherein said plurality of components are **independently** selected from **the group consisting of** a protein, a protein modification, a nucleic acid, a lipid, a carbohydrate, a sub-cellular structure, and an organelle.